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## SCIENTIFIC ARTICLE

# Factor XIII-guided treatment algorithm reduces blood transfusion in burn surgery



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### KEYWORDS

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### Abstract

**Background and objectives:** Major burn surgery causes large hemorrhage and coagulation dysfunction. Treatment algorithms guided by ROTEM<sup>®</sup> and factor VIIa reduce the need for blood products, but there is no evidence regarding factor XIII. Factor XIII deficiency changes clot stability and decreases wound healing. This study evaluates the efficacy and safety of factor XIII correction and its repercussion on transfusion requirements in burn surgery.

**Methods:** Randomized retrospective study with 40 patients undergoing surgery at the Burn Unit, allocated into Group A those with factor XIII assessment ( $n=20$ ), and Group B, those without assessment ( $n=20$ ). Erythrocyte transfusion was guided by a hemoglobin trigger of  $10\text{ g}\cdot\text{dL}^{-1}$  and the other blood products by routine coagulation and ROTEM<sup>®</sup> tests. Analysis of blood product consumption included units of erythrocytes, fresh frozen plasma, platelets, and fibrinogen. The coagulation biomarker analysis compared the pre- and post-operative values.

**Results and conclusions:** Group A (with factor XIII study) and Group B had identical total body surface area burned. All patients in Group A had a preoperative factor XIII deficiency, whose correction significantly reduced units of erythrocyte concentrate transfusion (1.95 vs. 4.05,  $p=0.001$ ). Pre- and post-operative coagulation biomarkers were similar between groups, revealing that routine coagulation tests did not identify factor XIII deficiency. There were no recorded thromboembolic events. Correction of factor XIII deficiency in burn surgery proved to be safe and effective for reducing perioperative transfusion of erythrocyte units.

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**PALAVRAS-CHAVE**

Cuidados intensivos;  
Queimados;  
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Coagulação e  
hemostase;  
Fator XIII

**Algoritmo de tratamento guiado pelo fator XIII reduz a transfusão sanguínea na cirurgia de queimados****Resumo**

*Justificativa e objetivos:* A cirurgia no grande queimado causa hemorragia de grande porte e disfunção da coagulação. Os algoritmos de tratamento guiados por ROTEM<sup>®</sup> e fator VIIa reduzem as necessidades de hemoderivados, mas falta evidência em relação ao fator XIII. A deficiência do fator XIII altera a estabilidade do coágulo e diminui a cicatrização. Este estudo avalia a eficácia e a segurança da correção do fator XIII e sua repercussão nas necessidades transfusionais na cirurgia do queimado.

*Métodos:* Estudo retrospectivo randomizado de 40 doentes submetidos à cirurgia na Unidade de Queimados alocados em grupo A com estudo do fator XIII ( $n=20$ ) e grupo B sem estudo ( $n=20$ ). A transfusão eritrocitária foi guiada por gatilho de hemoglobina de  $10\text{g}\cdot\text{dL}^{-1}$  e os outros hemoderivados por testes de coagulação de rotina e ROTEM<sup>®</sup>. A análise do consumo de hemoderivados incluiu unidades de eritrócitos, plasma fresco congelado, plaquetas e fibrinogênio. A análise dos biomarcadores da coagulação comparou os valores pré e pós-operatórios.

*Resultados e conclusões:* O grupo A (com estudo de fator XIII) e o grupo B apresentaram área de superfície corporal total queimada idêntica. Todos os doentes do grupo A revelaram déficit pré-operatório de fator XIII, cuja correção reduziu significativamente a transfusão de unidades de concentrado eritrocitário (1,95 vs. 4,05,  $p=0,001$ ). Os biomarcadores de coagulação pré e pós-operatórios foram semelhantes entre os grupos, revelaram que os testes de coagulação de rotina não identificam o déficit de fator XIII. Sem eventos tromboembólicos registrados. A correção do fator XIII na cirurgia do queimado revelou-se segura e eficaz na redução da transfusão perioperatória de unidades de eritrócitos.

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**Introduction**

Early excision and wound closure due to burn have allowed a reduction in mortality, lower rate of sepsis associated with burn, hypercatabolic response attenuation, blood loss reduction, as well as shorter hospital stay and associated costs. However, surgical treatment may also produce substantial intraoperative hemorrhage, both in debrided areas and donor sites, resulting in a significant increase in transfusion requirements. Furthermore, the loss and consumption of coagulation factors, associated with severe trauma and major surgery in the severely burned patient, together with hemodilution secondary to volume replacement contribute to reduce the plasma fraction of coagulation factors.<sup>1</sup>

The surgical technique improvement over the last years has allowed the reduction of intraoperative blood loss, but not significantly. Recent studies have shown that adequate and targeted correction of trauma-induced coagulopathy using specific blood products has reduced transfusion requirements and increased survival.<sup>2,3</sup> However, this therapeutic strategy has not yet been evaluated in burned patients.

It is in this context that factor XIII (FXIII), with a known and proven role in hemostasis and wound healing, has gained great interest. However, it is not detected by routine coagulation tests, such as prothrombin time and activated partial thromboplastin time, nor by patient bedside monitoring systems, which show results in real time, its dosage is determined in specialized laboratories.

In this study, our primary objective was to evaluate the need for perioperative transfusion after correcting the FXIII deficit in major burns and the secondary objectives were to evaluate the presence of FXIII deficiency and the efficacy and safety of its correction, particularly regarding the occurrence of thrombotic events.

**Methods**

Retrospective comparative study performed at the Burn Unit of our hospital between January 1, 2014, and December 31, 2015. It was submitted and accepted as a research project “*Estudo retrospectivo comparativo sobre a eficácia na correção pré-operatória do déficit de FXIII no grande queimado*” with reference number 94/16. All patients admitted to the Burn Unit during this period who had undergone at least one surgical intervention for surgical debridement with grafting under general anesthesia were considered eligible. We chose to perform a retrospective cohort analysis comprised of an intervention cohort, which included all patients with preoperative assessment and correction of FXIII (Group A) and a control cohort, in which a number of patients equal to that of Group A were randomly selected among all eligible patients (Group B).

Group A ( $n=20$ ) included patients with preoperative assessment and correction of FXIII and Group B ( $n=20$ ) included patients without FXIII assessment. Population characteristics were obtained by collecting data on age, sex, percent total body surface area (%TBSA) involvement,

number of surgeries and severity indexes, including the Simplified Acute Physiology Score II (Saps II) and Acute Physiology and Chronic Health Evaluation II (Apache II). We considered the first 24h after surgery as the perioperative period. The analytical parameters were collected and later evaluated in the Clinical Pathology Laboratory of our hospital, including hemoglobin (Hb) and hematocrit (Htc), collected in a PINK top tube (EDTA tripotassium) and evaluated in ADVIA 2120i™ equipment, and prothrombin time (PT), INR, activated partial thromboplastin time (aPTT) and fibrinogen (Fib) collected in a RED top tube (sodium citrate tube – citrated plasma) and analyzed by a coagulometric (turbodimetric) method using the ACL TOP™ equipment. On its turn, the Factor XIII assay started with the collection of blood sample in a RED top tube (sodium citrate tube – citrated plasma), centrifuged at  $3000 \times g$  for 15 min using the Hemosil® Factor XIII Antigen reagent (0020201300) and evaluated using the ACL TOP™ equipment.

These parameters were evaluated in the pre- and post-operative periods. The transfusion trigger for Hb correction through transfusion support with packed red blood cells (pRBC) units was  $10 \text{ g.dL}^{-1}$ . Factor XIII concentrate was used to correct its deficit through the reference values for a healthy population, and the remaining blood products were administered guided by the standard coagulation tests and ROTEM®, performed in the perioperative period. The number of blood products administered during the perioperative period was recorded in the database. Due to the difficulty in its quantification, blood losses were not evaluated and there were also no data available on wound healing and graft survival.

FXIII quantification and number of blood products administered were the parametric outcomes evaluated for the aforementioned purposes.

## Statistical analysis

In order to select the statistical test adequate to the consumption of blood products, the normality of the two parameters with a longer interval was evaluated: “pRBC administered” and fresh frozen plasma (FFP) pRBSC “FFP administered”. Shapiro–Wilks test ( $n = 20$  per group) showed normality in Group B ( $p = 0.407$ ) but not in Group A ( $p = 0.042$ ). Regarding the units of “FFP administered” both groups were not normally distributed ( $p < 0.001$ ). However,

after quantile–quantile plot analysis and given the reliability of Student’s *t*-test, the latter was selected. Regarding the remaining blood products (PC and Fib) consumption, and due to its short interval, the dichotomization between administered and non-administered was preferred; Fisher’s exact test was performed. Multiple analyzes of coagulation biomarkers were performed using Mann–Whitney test to compare groups by their pre- and post-operative values (Hb, Htc, PT, INR, aPTT, Fib and FXIII) and Wilcoxon signed-rank test for paired comparison. Adverse effects related to FXIII administration were also monitored.

## Results

Forty patients were included in the study: 20 in Group A undergoing FXIII assessment and administration and 20 in Group B not undergoing FXIII assessment and administration. Table 1 shows the characteristics of patients. It is worth noting that most patients were male in both samples (75% total), Saps II in Group B was significantly higher than in Group A (A – 39.5 and B – 53,  $p < 0.001$ ), such as age (A – 40 and B – 46,  $p = 0.009$ ). There were no statistically significant differences in the other parameters.

Student’s *t*-test demonstrated a significant difference ( $p = 0.001$ ) between the two groups regarding the “administered pRBC”, with 1.95 (95% CI 1.46–2.44) in Group A, compared to 4.05 (95% CI 2.93–5.17) in Group B. The adopted transfusion threshold Unit of  $10 \text{ g.dL}^{-1}$  was adapted to the major burn patient. However, no statistical difference was observed between the two groups for the remaining blood products (Table 2 and Fig. 1).

Multiple analyzes were performed to compare the two groups regarding the coagulation biomarkers in the pre- and post-operative periods, but there were no statistically relevant differences between both groups, except for pre- and post-operative fibrinogen in both groups. All patients in Group A had FXIII deficiency ( $M = 46.6\%$ , 95% CI 39.9–53.3), according to laboratory reference values for the general population ( $\geq 70\%$ ), with significant elevation after correction ( $p < 0.005$ ). There was no significant difference for pre- and post-operative Hb in both groups, as well as between groups (Table 3).

There were no complications associated with the use of FXIII. Thrombotic events were not recorded.

**Table 1** Population characteristics.

<i>n</i>	Group A 20	Group B 20	<i>p</i>	Total 40
Median age (1st and 3rd quartiles)	40 (24/43)	46 (41/61)	0.009 <sup>a</sup>	42 (27/56)
Male, <i>n</i> (%)	17 (85%)	13 (65%)	0.144 <sup>b</sup>	30/10 (75–25%)
Median %TBSA (1st and 3rd quartiles)	50 (23/51)	45 (18/55)	0.547 <sup>a</sup>	47.5 (21/51)
Median number of surgeries (1st and 3rd quartiles)	3.5 (1/6)	3 (2/6)	0.925 <sup>a</sup>	3.5 (2/6)
Median Saps II (1st and 3rd quartiles)	39.5 (25/43)	54 (42/75)	<0.001 <sup>a</sup>	43 (34/54)
Median Apache II (1st and 3rd quartiles)	23 (12/26)	18.5 (9/28)	0.445 <sup>a</sup>	21.5 (10/28)

TBSA, total body surface area; Apache II, Acute Physiology and Chronic Health Evaluation II; Saps II, Simplified Acute Physiology Score II.

<sup>a</sup> Mann–Whitney test.

<sup>b</sup> Chi-square test.

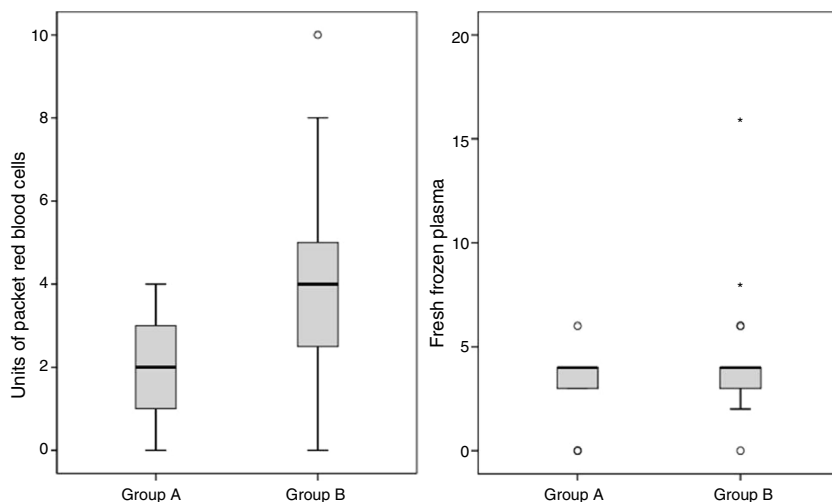
**Table 2** Transfusion requirements in groups A (with factor XIII) and B (without factor XIII).

N	Group A 20	Group B 20	p
Mean pRBC used (95% CI)	1.95 (1.46–2.44)	4.05 (2.93–5.17)	0.001 <sup>a</sup>
Mean FFP used (95% CI)	3.50 (2.86–4.14)	4.40 (2.91–5.89)	0.252 <sup>a</sup>
Number of platelets used (%)	1 (5%)	5 (20%)	0.342 <sup>b</sup>
Number of fibrinogen concentrate used (%)	1 (5%)	3 (15%)	0.605 <sup>b</sup>

95% CI, 95% confidence interval; FFP, fresh frozen plasma; pRBC, units of packed red blood cells.

<sup>a</sup> Student's *t*-test.

<sup>b</sup> Fisher exact test.



**Figure 1** Distribution of packed red blood cell and fresh frozen plasma units used in groups A (with FXIII) and B (without FXIII).

## Discussion

The surgical approach to burns is often associated with significant hemorrhage requiring the administration of blood products<sup>4</sup> and consequent increase in associated morbidity and mortality, well described and known in the critically ill patient.<sup>5–9</sup>

Despite the various methods developed to reduce intraoperative hemorrhage, notably the topical application of adrenaline, both in the burn areas and donor sites, subcutaneous infiltration of vasoconstrictors (adrenaline, phenylephrine or vasopressin),<sup>10–15</sup> systemic administration of vasopressin, controlled hypotension, laser excision,<sup>16</sup> or tourniquet application, there is still a high need for transfusion support, particularly packed red blood cells (pRBC), fresh frozen plasma (FFP), platelet concentrate (PC) or prothrombin complex (PTC),<sup>17–21</sup> whose use aggravates the outcome of critically ill patients due to the increase in infectious complications, multiple organ failure, and Acute Respiratory Distress Syndrome (ARDS)/Transfusion-Related Acute Lung Injury (TRALI).<sup>5–9</sup> Thus, reducing blood loss and need for blood product administration may improve outcome and safety in these patients.

Recently, and with the increasing offer of functional coagulation tests and bedside testing, the interest in improving and correcting coagulation cascade changes has increased.

In this context, the role of factor XIII has been poorly studied. FXIII is a plasma transglutaminase essential for normal hemostasis at the end-stage of the coagulation cascade. It is responsible for the intermolecular binding reactions between fibrin monomers, inhibition of  $\alpha$ 2-antiplasmin, and binding to subendothelial collagen and fibronectin.<sup>22</sup> These reactions increase the mechanical strength of fibrin clot and confer resistance to proteolytic degradation, in addition to promote clot adhesion to the vascular matrix.<sup>23,24</sup> This factor deficiency results in hemostasis disorder due to clot anomalous formation, secondary to the fragile binding between fibrin monomers and low clot resistance against fibrinolysis. This coagulation factor is decreased in burn patients. However, this deficit causes no changes in classic coagulation tests.

The objective of our retrospective analysis was to describe our unit's experience in correcting FXIII levels and the impact of this correction on transfusion requirements, based on an Hb target value equal to or greater than  $10\text{g.dL}^{-1}$ , accepted for major burn patients, with critical illness and/or cardiopulmonary impairment.<sup>25,26</sup>

It was found that all patients tested had FXIII deficiency in the measurements performed during hospitalization. There was a statistically significant difference in the amount of pRBC administered in the FXIII replacement group (1.95 vs. 4.05 for Control Group), even with the preoperative values of Hb slightly lower than in the FXIII replacement group

**Table 3** Pre- and post-operative paired comparison – tests of groups A (with factor XIII) and B (without factor XIII).

Variable	Pre–mean (95% CI)	Post–mean (95% CI)	<i>p</i> <sup>a</sup>
<i>Hemoglobin (g.dL<sup>-1</sup>)</i>			
Group A	9.80 (9.40–10.20)	9.96 (9.60–10.31)	0.432
Group B	10.39 (9.87–10.92)	10.1 (9.45–10.74)	0.304
<i>p</i> <sup>b</sup>	0.121	0.989	
<i>Hematocrit (%)</i>			
Group A	29.4 (28.3–30.5)	29.3 (28.1–30.5)	0.794
Group B	31.1 (29.4–32.8)	29.7 (27.7–31.6)	0.147
<i>p</i> <sup>b</sup>	0.086	0.883	
<i>aPTT (sec)</i>			
Group A	29.9 (28.6–31.3)	29.8 (28.7–30.8)	0.667
Group B	30.6 (29.1–32.1)	30.7 (28.9–32.4)	0.698
<i>p</i> <sup>b</sup>	0.640	0.659	
<i>PT (sec)</i>			
Group A	12.4 (11.8–12.9)	12.1 (10.7–13.6)	0.102
Group B	13.1 (11.9–14.4)	13.9 (12.5–15.3)	0.064
<i>p</i> <sup>b</sup>	0.947	0.327	
<i>INR (sec)</i>			
Group A	1.07 (1.02–1.12)	1.11 (1.06–1.16)	0.022
Group B	1.13 (1.04–1.21)	1.21 (1.08–1.33)	0.087
<i>p</i> <sup>b</sup>	0.445	0.512	
<i>Fibrinogen (g.L<sup>-1</sup>)</i>			
Group A	554(462–646)	421(349–493)	<0.001
Group B	429(373–485)	372(322–422)	0.007
<i>p</i> <sup>b</sup>	0.021	0.718	
<i>Factor XIII (%)</i>			
Group A	46.6 (39.9–53.3)	61.6 (58.1–65.7)	<0.001
Group B	–	–	
<i>p</i> <sup>b</sup>	–	–	

aPTT, activated partial thromboplastin time; FXIII, factor XIII; INR, international normalized ratio; PT, prothrombin time.

<sup>a</sup> Wilcoxon signed-rank test for pre-post comparison.

<sup>b</sup> Mann–Whitney test for comparison between groups.

(at about 0.5 g.dL<sup>-1</sup>). The transfusion threshold was considered in both groups, so the decreased need for pRBC in Group A would not be justified by the existence of a different transfusion threshold between groups, as the pre- and post-operative Hb values were similar. However, the same did not occur for the remaining blood products. For explanation, we consider the following hypotheses: (1) Our patients received fresh frozen plasma preoperatively and as such did not significantly differ from the amount administered. (2) Since there were no changes in the coagulation tests, there was no need for administration of other blood products other than packed red blood cells.

We also admit the fact that Group B is composed of a population with a significantly higher Saps II value that present more comorbidities than coagulation changes may have contributed to this difference in transfusion requirements, although the same has not been verified in Apache II.

Transfusion requirements were only recorded in the early postoperative period (up to 24h), this difference may be even greater if the entire hospital staying with stabilization of FXIII levels is considered. It is also worth noting the difference between the number of surgeries in both groups,

which makes it possible to hypothesize the role of factor XIII not only in reducing the consumption of pRBC but also in successful grafting with a consequent reduction in the need for multiple surgeries.

We recognized other limitations in our analysis: the population of both groups was identical in terms of burned body surface area — a factor of greater impact for bleeding risk, but it would be ideal to characterize the population both in terms of duration of surgeries and quantification of intraoperative bleeding losses. Regarding the results obtained, we indicated as a limitation the lack of correlation with the amount of pRBC units used throughout hospitalization and whether this decrease was correlated with ventilation time, ARDS/TRALI incidence, hospital stay, or impact on mortality.

## Conclusion

FXIII is regarded in our clinical reality as a still poorly used blood product, perhaps due to its high cost in the pharmaceutical market.

In this study, there was a statistically significant reduction in the perioperative consumption of pRBC after an

effective and safe correction of FXIII deficiency in major burn, present in all patients.

At a time when the goal is to adopt a progressively more conservative transfusion attitude (because of the well-recognized risks of heterologous transfusion), it is imperative to consider the use of FXIII. It will have a positive economical and clinical impact on the final outcome by reducing transfusion, and, therefore, the consequences of heterologous transfusion that is too liberal particularly in an immunocompromised population such as the burn patients.

## Conflicts of interest

The authors declare no conflicts of interest.

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